NASA TECHNICAL MEMORANDUM

NASA TM-76196

EXPERIMENTAL CORONARY SCLEROSIS INDUCED BY IMMOBILIZATION OF RABBITS. A NEW MODEL OF ARTERIOSCLEROSIS

V. V. Tyavokin

Translation of "Experimentelle Coronarsklerose durch Bewegungseinschränkung beim Kaninchen, Ein neues Modell der Arteriosklerose," Virchows Archiv, Abteiling A, Pathologische Anatomie, Vol. 346, 1969, pp 29-45.

(NASA-TM-76196) EXPERIMENTAL CORONARY SCLEROSIS INDUCED BY IMMOBILIZATION OF RABBITS: A NEW MODEL OF ARTERIOSCLEROSIS (National Aeronautics and Space Administration) 19 p HC A02/MF A01 CSCL 06C G3/51

N80-27990

Unclas 28029

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D. C. JUNE 1980

STANDARD TITLE PAGE

1. Report No. NASA TM-76196	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle EXPERIMENTAL CORONARY SCLEROSIS INDUCED BY IMMOBILIZATION OF RABBITS. A NEW MODEL OF ARTERIOSCLEROSIS		5. Report Date June 1980 6. Performing Organization Code
7. Author(s) V. V. Tyavokin * ALSO W. W. TJAWOKIN		8. Performing Organization Report No. 10. Work Unit No. 11. Contract or Grant No. NASw-3199
9. Performing Organization Name and Address Leo Kanner Associates Redwood City, California 94063		13. Type of Report and Period Covered Translation
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration Washington, D. C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes

Translation of "Experimentelle Coronarsklerose durch Bewegungseinschränkung beim Kaninchen, Ein neues Modell der Arteriosklerose," Virchows Archiv, Abteilung A, Pathologische Anatomie, Vol. 346, 1969, pp 29-45.

16. Abstract A new method for producing arteriosclerosis with coronary insufficiency in rabbits by means of immobilization. The experimentally induced atherosclerosis develops due to hypodynamics imposed by the reduced muscular activity without overloading with exogenous cholesterol. The atherosclerosis and coronary insufficiency are associated. With variations in the duration and extent of immobilization, coronary insufficiency alone or with atherosclerosis can be produced. This new method for producing arteriosclerosis and ischemic cardiac disease has its clinical counterpart.

17. Key Words (Selected by Author(s))	18. Distribution Statement
	Unclassified-Unlimited

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	19	

EXPERIMENTAL CORONARY SCLEROSIS INDUCED BY IMMOBILIZATION OF RABBITS. A NEW MODEL OF ARTERIOSCLEROSIS

V. V. Tyavokin[1]

We reported earlier on the possibility of producing arteriosclerosis with coronary insufficiency in rabbits by restricting their mobility (1965, 1965a, b, 1967a, b). In new experiments where mobility is even more severely restricted we wish to attempt an analysis of the experimental findings. /29*

Material and Method

The experimental animals were male chincilla rabbits kept in cages specially designed for immobilization (1966). The position of the animals was not changed during feeding and during the required blood chemistry and EKG examinations. At specific time intervals we checked blood cholesterol, blood corticosteroids and GOT activity in the blood serum. At the end of the experiment the arterial blood pressure was taken. Macroscopic and microscopic alterations in the aorta and microscopic alterations inthe myocardium were assessed in animals that underwent acute demise during the experiment as well as those sacrificed by a cervical blow at the end of the experiment. This was done according to a specific grading. /30

79 animals were divided into 3 groups. The actual experimental group contained 58 animals. A first control group numbering 12 animals were kept in ordinary cages for the duration of the experiment (23-55 days). A second control group numbering 9 animals lived for 12 months in similar cages. All animals received normal food.

Results

The type and extent of morphological changes in the aorta, coronary arteries and myocardium as well as the EKG findings are given in the Table. In the actual experimental group 58 animals started out and 30 died acutely before the end of the exper-

---

* Numbers in the margin indicate pagination in the foreign text.

TABLE. CHANGES IN AORTA, CORONARY ARTERIES, MYOCARDIUM. EKG FINDINGS FOR TEST ANIMALS AND CONTROLS.

Group	Serial No.	Rabbit wt in g		Immobile period	Morphological changes			Degree of EKG changes	Arterial pressure mm Hg	Remarks
		Start	Finish		Aorta	Coronary arteries	Myocardium			
1	2	3	4	5	6	7	8	9	10	11
Test group	1	4300	4250	died day 1	+					
	2	2800	2650	24 days	++++ Aneur. in abd. region	++++	++++	IV. Myoc. infarct	100	prefinal pulm. edema
	3	2900	2750	died day 12	++++	++++	++++	as in 2		
	4	4100	3950	d. day 11	++++	++++	++++	as in 2		as in 2
	5	3800	3750	d. day 1	+					
	6	2900	2500	20 days	+++			Coronary insuffic. III	104	
	7	3300	3250	d. day 7	+					as in 2
	8	3150	2950	d. day 18	++	++	++++	as in 2		
	9	3050	2950	13 days	++			as in 2	84	
	10	3150	3100	28 days	+++			as in 6	106	as in 2
	11	3500	3450	22 days	++++ as in 2			as in 2	82	as in 2
	12	2800	2600	d. day 9	+		+++	as in 6		as in 2
	13	2400	2350	14 days	++++			as in 6	96	
	14	3100	3050	d. day 13	++++ as in 2					as in 2

/36,37

2	3	4	5	6	7	8	9	10	11
15	3000	2900	d. day 10	++++ Ulcer-ations					as in 2
16	2900	2850	21 days	++++ as in 2			as in 2	82	
17	3100	2950	d. day 12	++++ as in 2	+	+++	as in 6		as in 2
18	2600	2600	21 days	++++			as in 6	98	
19	2850	2800	d. day 10	++++	++	+++	as in 6		
20	2650	2600	19 days	++			as in 6	102	
21	3050	3000	d. day 3	+	++	++++	as in 2		as in 2
22	2900	2850	10 days	+			as in 2	83	
23	2700	2750	10 days	+			as in 6	106	
24	3200	3100	10 days	++++ Increase in abd. region			as in 2	80	
25	2600	2550	7 days	+			II.Coron. insuffic.	98	
26	2750	2725	7 days	+			as in 25	106	
27	3050	3000	d. day 4	+					as in 2
28	2900	2875	d. day 7	++					
29	3600	3450	28 days	++++ as in 2			as in 6	104	
30	3200	3000	30 days	+		+	I	110	Mild motor restriction

2	3	4	5	6	7	8	9	101	11
31	4100	3950	20 days	+++					as in 2
32	4000	3900	d. day 2	+	++++	+++			as in 2
33	4300	4250	d. day 1	+	+++	+++			
34	2900	2650	29 days	++++ as in 2	++++	++++	as in 6	104	
35	2800	2850	28 days	+			I	108	as in 30
36	3600	3500	20 days	++++ as in 2			as in 2	102	
37	3400	3425	24 days					108	as in 30
38	3450	3375	d. day 16	+++					
39	2900	2700	20 days	++	++++	+++	as in 6	100	
40	3325	3300	22 days	++++ as in 2			as in 2	82	
41	3100	3050	d. day 11	++					as in 2
42	3500	3425	d. day 10	++					as in 2
43	3800	3725	d. day 6	+++ Stage before atheromatose breakup in abdom. region					as in 2
44	3650	3600	11 days	++	+++	+++	as in 6		
45	3600	3000	15 days	++			as in 6	96	
46	3200	3100	15 days	++			as in 6	104	

/39
/40

2	3	4	5	6	7	8	9	10	11
47	4900	4500	15 days	+			as in 6	88	
48	3650	3400	d. day 12	+			as in 2		as in 2
49	3300	3100	d. day 5				as in 2		as in 2
50	3700	3600	d. day 9	++			as in 6		as in 2
51	3600	3550	d. day 2	+	+++	+++	as in 6		as in 2
52	5000	4700	d. day 14	++			as in 6		as in 2
53	3400	3500	d. day 10	++			as in 6		
54	3700	3600	d. day 13	++++ nodular ulcera-tion			as in 2		as in 2
55	3200	3150	d. day 5	+		+++	as in 6		
56	3600	3450	d. day 6	+			as in 2		
57	3200	3050	10 days	+			II. Coron. insuffic.		
58	3050	3000	12 days	++			as in 57		

	1	2	3	4	5	6	7	8	9	10	11
Control group I		59	3200	3250						98	
		60	2900	2950						108	
		61	2700	2800						97	
		62	3000	3050						92	
		63	3150	3200						88	
		64	2850	2875						103	
		65	2600	2625						92	
		66	3100	3100						88	
		67	2825	2850							
		68	2600	2625							
		69	2900	2950							
		70	2850	2875							
Control group II		71	2900	3250							
		72	3050	3400							
		73	2850	3275							
		74	2850	3450						108	
		75	3100	3425						90	
		76	2950	3250						94	
		77	2900	3200						102	
		78	3025	3275							
		79	2825	3350							

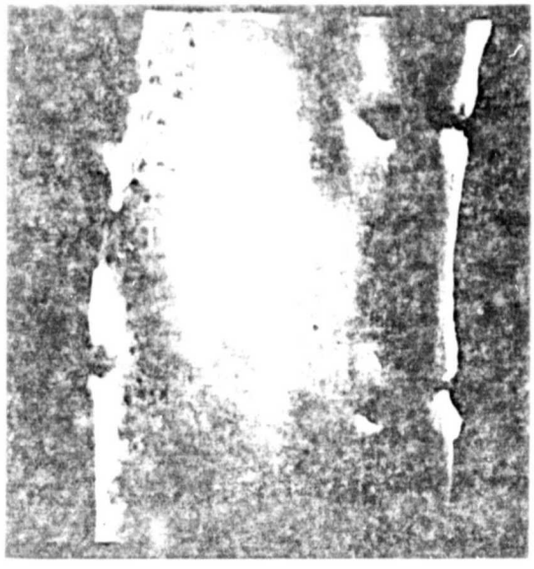

Fig. 1. Aorta (animal No. 15). Focal ulceration of the intima following 10 days of experiment.

iment. Shortly before demise 22 of these developed pulmonary edema. Nearly all animal in this group (except 2) showed distinct macroscopic alterations in the aorta in the form of roughened endothelium, arteriosclerotic nodules, atheromatose ulcerations and aneurisms. The extent of morphological changes was represented by this grading: rough endothelium = +, thickening of the intima to a lesser degree = ++, thickening of the intima to a large extent = +++ and ulcerous breakup = ++++.

Roughness of the endothelium was shown also by animals that died acutely already on the first day of the experiment (Nos. 1, 5, 33). We may distinguish two different forms of roughened endothelium: in the first case there is incipient thickening of the intima and in the second case incipient breakup of the intima. The majority of animals showed a development of ulcerous breakup prior to arteriosclerotic thickening of the intima. Fig. 1. shows focal ulcerations of the aorta on day 10. Only in rare cases did nodules and ulcers develop side by side at the same time (Fig. 2a, b). In the case of 10 experimental animals of one /31
group of 41 kept under particularly severe conditions of immobilization did an aneurism develop in the abdominal aorta (Fig. 3).

Three animals of group I were subjected to less severe conditions and were allowed to move their legs (Nos. 37, 35, 30). These were sacrificed on days 24, 28 and 30. Only animal No. 30 showed slight changes in the intima of the aorta (+). The two others showed absolutely no macroscopic changes. Out of all the animals in both control groups 2 animals of group III showed nodule formation in the aorta (++).

Already during day 1 of the experiment we were able to find histological chan- /32
ges of the aorta and endothelium in part of the animals. The layer of endothelial cells ran an uneven and rough course. More obvious changes were developing in the subendothelial tissue and this independently of prior endothelial changes. At the

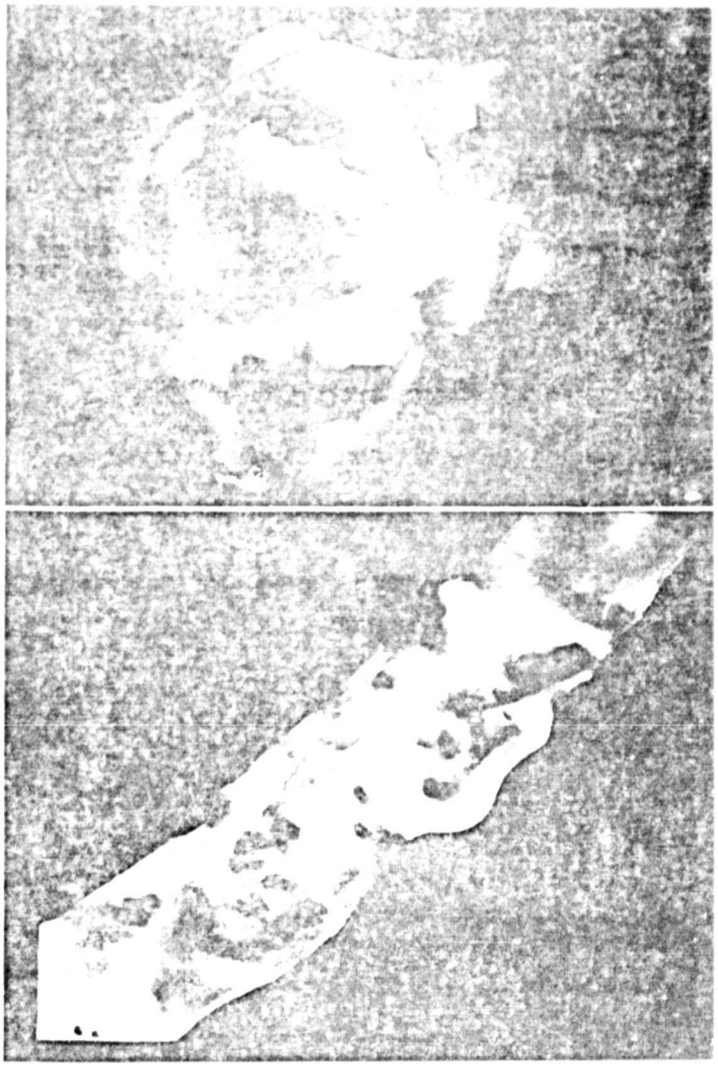

Fig. 2a, b. Aorta (animal No. 29) 28 days after initiation of immobilization. a - focal intima nodules in aortal arch; b - extende intima ulceration in abdominal aorta.

beginning of an arteriosclerotic nodule there is a subendothelial edema that gradually increases and incorporates cloudy sudanophilic substances. The amount of these substances runs a parallel course with proliferation of subendothelial cells. The cells, which vary in size and shape, go on to accumulate fats. Not infrequently cells crammed full of fat masses break up in the center of the nodules. Over the arteriosclerotic nodules and in their immediate vicinity the endothelium often detaches itself from its basement (Fig. 4a, b). Finally the progressive shrinking of the detached endothelium layer is accompanied by the breakup of endothelium and the formation of ulcers.

In 13 of 17 animals examined in group I there were also similar changes in the coronary arteries. As in the aorta, the initial situation is subendothelial edema. However, in contrast to the aorta we noted here no deposit of sudanophilic substances. Moreover, cell proliferation was distinctly weaker than in the case of the aorta. More severe immobilization in this case also clearly produced increased peremeability of the endothelial layer to blood proteins. Depending upon the extent of changes there was compression or complete occlusion of the vascular lumina. Vascular stenosis and vascular occlusion developed in arteries of different caliber. When mobility was restricted for 10-20 days the animals exhibited different forms and degrees of changes in the coronary vessels ranging from

Fig. 3. Aorta (animal No. 36) 20 days after beginning of experiment. Aneurism of abdominal aorta at diaphragm level, middle occupied by ulcerations and ulcerous nodules.

subendothelial edema to sclerosis with /33
total occlusion of the vessels (Fig. 5).

Changes of the myocardium began with hemostasis in the capillaries. Frequently there was circumscribed diapedesis. Muscle fibers in the early stages showed a loosening of the fribrils, a loss of cross striation and a loss of the capacity for nuclear coloration. In more prolonged experiments the muscle fibers ac- /34
cumulated fat. There was frequent development of circumscribed myocardial necroses, as in the case of 6 out of 7 animals of group I. The argyrophilic fiber network became collagenized and the destroyed muscle fibers were replaced by connective tissue. In the Table we have rated myocardial alterations as follows: circumscribed loss of nuclear colorability and cross striation, depending upon extent, from + to ++. Extensive changes of this kind +++. Focal necroses ++++.

In the case of 7 animals we made a neurohistological examination of the nerve fibers of the aorta and in 5 animals an examination of the heart fibers. The extent of recognizable changes ranges from reactive to severely degenerative. It is worthy of note, that neural changes in the aorta and heart are distinctly inferior in extent to those of arteriosclerosis and coronary insufficiency. Consequently in our experiments we consider neural changes as secondary. They are the result of the conditions in the organism which have induced the development of arteriosclerosis and coronary insufficiency. On the other hand it seems possible, that the neural changes have a regressive effect on the course of arteriosclerosis. This might be an explanation for the breakup of ulcerations since in the area that they occupied we found no neural tissue. We are apparently dealing here with a vicious circle.

The EKG findings are parallel to the microscopic myocardial changes. Nearly all examined rabbits in group I (except for 3) showed marks of coronary insufficiency:

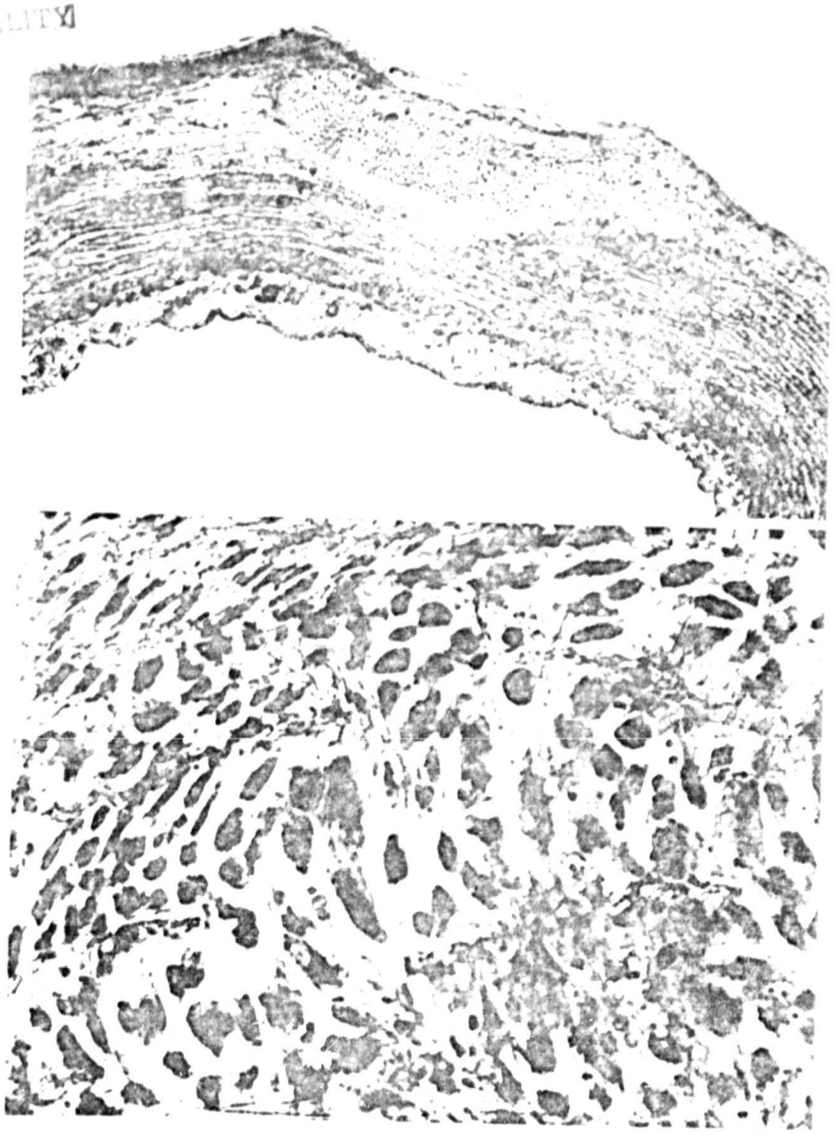

Fig. 4a, b. Aorta (animal No. 14) 11 days after beginning of experiment. a - detached endothelium with subendothelial cell proliferation, x 50; b - cell fattening, incipient cell destruction, x 450. Hematoxylin-sudan III.

displacement of the ST line, deformation of the T wave. We distinguish 4 degrees of EKG changes:

1. Broadening of the T wave;
2. A higher degree of T wave changes with negativization; /35
3. Concordant displacement of the RST complex;
4. Signs of myocardial infarct.

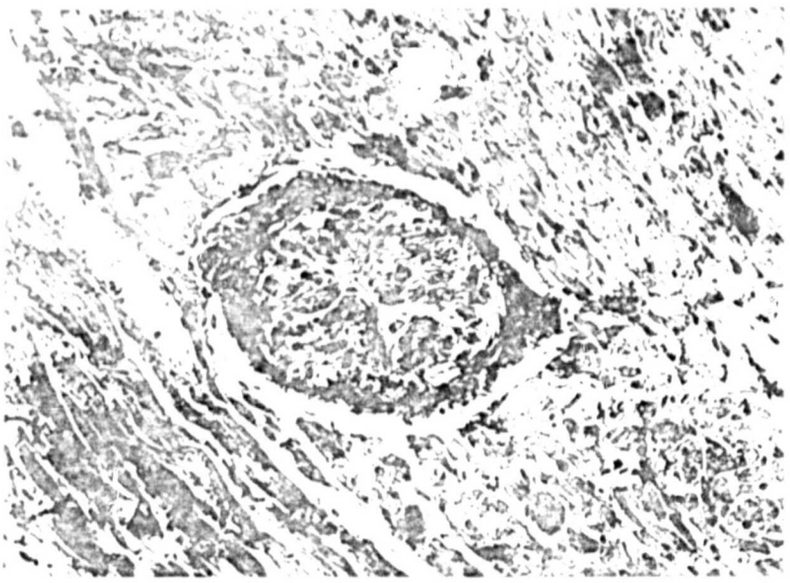

Fig. 5. Cardiac muscle (animal No. 35) 20 days after beginning of experiment. Sclerosis of coronary artery branch with total occlusion of vascular lumen, x 240. van Gieson.

Of special interest is the EKG of 3 rabbits (Nos. 30, 35, 37) whose movements were less restricted. Although they were sacrificed later than the other animals, following days 24, 28 and 30, the EKG of animals No. 30 and 35 showed only changes of the first degree and for animal No. 37 none at all. Among the animals whose mobility was severely restricted (41 animals) 4 showed changes of the second degree, 21 changes of the third and 16 of the fourth degree, with signs of myocardial infarct.

In order to study further the myocardial changes we used GOT activity in the blood serum. At the beginning and end of the experiment we determined this activity for 20 experimental animals using the colorimetric procedure of Reitmann and Frenkel (1957). 10 animals showed histological changes in the form of myocardial infarcts, 8 showed changes of the third degree and 1 no changes at all. The initial mean activity level was 12.3±1.9 col. E. At the end of the experiment this level for animals with histological coronary infarct was around 37.4±18.8 col. E. The activity fluctuated between 12.6 and 125.6 col. E. In a group with myocardial changes of the third degree the mean activity level was 44.5±7 col. E. Activity fluctuated between 15.7 and 88 col. E. Difference of activity for GOT at the beginning and end of the experiment is statistically significant in both groups ($P < 0.001$).

If we compare the GOT activity of both groups at the end of the experiment we also find a statistically reliable difference ($P < 0.025$). In regard to arterial blood pressure there is no assessable difference between experimental and control animals.

At the beginning of the experiments the cholesterol level in the blood serum was 81±1.43 mg%. After 24 hours the mean value was 75±8.85 mg% ($P > 0.2$). After 5 days it was 89±9.6 mg% ($P > 0.2$), after 7-10 days 63±7.7 mg% ($P < 0.015$), after 14-15 days 82±9.6 mg%, after 28-30 days 176±15.08 mg% ($P < 0.01$).

There were considerable fluctuations in the average cholesterol level during the first 2 weeks. The majority of animals showed high cholesterol at the beginning of the experiment. This decreased as the experiment went on. After 7-10 days the drop was significant statistically. When the experiment lasted longer there was a new increase. After 14-15 days there was a return to the initial value, after 28-30 days this value was distinctly exceeded. In the case of 22 experimental animals we examined the amount of corticosteroids in the blood. At the beginning of the experiment the mean value was 11.87±0.25 gamma/100 ml plasma. After 24 hrs it was higher by a very slight and therefore statistically insignificant amount. It is noteworthy that this increase is true only for 2 animals who showed a blood level of 24.3 and 20.5 gamma/100 ml plasma. For the other rabbits the corticosteroid level remained the same. After 4, 7 and 14 days only did the average value go down to 10.57±0.89 /42 ($P < 0.05$), 9.21±0.92 ($P < 0.005$) and 8.9±0.86 gamma/100 ml plasma ($P < 0.001$).

In the case of 14 experimental animals and 16 controls we examined likewise the catecholamine content of the myocardium of the base of the heart. The mean adrenal level of the control group was 0.788± 0.0497 mg and the norepinephrine level 0.583± 0.0083. The experimental group showed an average adrenalin value of 0.5812±0.0227 ($P < 0.001$) and an average norepinephrine value of 0.3417±0.0258 ($P < 0.001$).

Discussion of Findings

An experimental creation of arteriosclerosis with coronary insufficiency in the rabbit by means of severe mobility restriction offers a new model for experimental research in sclerosis and myocardial infarct. In a model under discussion which factors induce arteriosclerosis and coronary insufficiency? Are we dealing with a neurally generated event or a direct consequence of abrogated muscular activity?

Undoubtedly at the beginning of the experiments there is nervous excitation in the animals. After 2-3 days this fades as they become habituated to their cramped

position. Shutova (1958, 1963) and Chomulo (1961, 1964) have pointed out the significance of prolonged functional excitation of the central nervous system in respect to arteriosclerosis in rabbits. In our experiment the chief factor in sclerosis is the hypodynamia consequent upon the external restriction of muscular activity. The following facts support this position:

1. Arteriosclerosis and coronary insufficiency do not develop after long experiments. Distinct changes in the aortal wall are seen already during the first week of the experiment. They lead to characteristic arteriosclerotic nodules and ulcerous breakups in relatively short periods of time (10, 15, 20, 30 days). Up to now there have been no reports on similar experimentally induced changes in the aorta wall. The experiments of Chomulo lasted many months and even years. It took him 23 months of excitation of the central nervous system without additional exogenous cholesterol overloading alone to produce lipoidosis in the vascular walls of the rabbit.

2. Our results show a clear association between the extent and length of mobility restriction on the one hand and morphological changes in the aorta wall and myocardium on the other. The longer and more consistently severe the immobilization, the more pronounced the changes in the aorta and myocardium.

3. In our experiment the most prominent changes occur in the area of the lumbar aorta. This is a part of the body most clearly affected by immobilization due to the construction of the cages. Out of 41 animals subjected to particularly severe immobilization 10 showed an aneurism of the abdominal aorta.

4. Only 2 out of a total of 9 control animals kept in ordinary cages for 12 months presented sclerotic nodules of the aorta wall. In this case the influence of neural factors is excluded because of experimental conditions.

5. Three of the experimental animals were kept in less severe immobility al- /43
lowing for leg movement. They were sacrificed later than most of the other animals (after 24, 28 and 30 days). Only one of them presented changes in the aorta of the first degree of severity (+). Undoubtedly a neural factor is at work in this experimental method. Since immobilization is not severe a higher grade of atherosclerosis cannot develop.

6. During the experiments the corticosteroid level in the blood declined.

7. There was a statistically reliable reduction of catecholamines in the myocardium. Gavyrin (1961, 1966) was able to demonstrate that elimination of the sympathicus induces distinct morphological changes in the myocardium of vertebrates, whereas the reinforcement of sympathetic stimulation induces no visible degenerative changes in the heart muscle. Our results are in accord with this finding. Immobilization in the rabbit leads to a reduction of catecholamines in the myocardium and thus conditions secondary changes in the heart muscle.

8. The morphological changes in the nervous system of the aorta and of the heart are distinctly less pronounced than those that occur in association with developing arteriosclerosis and coronary insufficiency.

Thus the restriction of muscular activity (hypodynamia) in our experiments must be considered as the chief factor of the developing arteriosclerosis and coronary insufficiency. We have not found any further reports in the literature demonstrating comparable severe changes in the coronary arteries experimentally induced. Only Selye (1961) noted the development of a sharply delineated occlusive subintimal edema with focal necroses of the myocardium in rats presenting mild sclerosis of the coronary vessels induced by an overdose of vitamin D derivatives and the administration of 2-methyl-9-chlorcortisol and NaH_2PO_4. Meessen (1944), Büchner (1946), Bredt (1949) and Müller (1949) reported on fatal myocardial infarcts which developed in the subintimal layers of the coronary arteries following nonadipose edema.

Doerr (1963) presented the intramural movement of the perfusion stream in the aorta. He was able to demonstrate that the reorganization of the inner wall structure resulted in blockage of the plasmatic perfusion stream with consequent accumulation of lipoids. Our findings in respect to disturbed plasma perfusion and edema in experimental arteriosclerosis coincide with these research results.

Quite obviously the movement of the vascular canal is essential for maintaining its structure and nourishment. In humans the most severe mobility restriction in the aorta occurs in the region of the aorta arc. This is probably why in humans arteriosclerosis develops at this part of the aorta most frequently and most severely. In

our experiments movement restriction of the aorta canal occurred especially in the abdominal area. This was also the area in which the most prominent changes in the wall developed. According to our findings, blockage of the intramural perfusion stream predominates in the abdominal aortas. On the other hand subintimal edematous swelling predominates in the coronary arteries, which move periodically during the operation of the heart. /44

Green (1935) observed that there is an increase in coronary blood flow that sets in with the contraction of isolated muscles which are only attached to the organism by nerves. Lebedinskiy, Medved'yev and Peymer (1953) found that muscle contraction due to the excitation of proprioreceptors releases reflexively an increase in coronary flow of blood. In their experiments with cats they found that muscular contraction of the extremities due to excitation of the cerebral cortex was accompanied by an increased flow of coronary blood. There was no such increase when the roots of the posterior spinal chord were severed so that impulses from the proprioreceptors of contracting muscles could not reach the nervous system. Evidently in the case of the rabbit in hypokinesia there is a reduction in the reflex effects on the coronary vessels, so that, in addition to the factors mentioned above, a restriction on the myocardial blood supply is effected.

Our experimental results indicate that arteriosclerosis and coronary insufficiency are to be considered homogeneously. Coronary insufficiency should not be looked upon merely as a complication of coronary sclerosis. In our experiments with rabbit immobilization it is possible, by modifying experimental conditions in respect to the extent and length of immobilization to produce coronary insufficiency without arteriosclerosis as well as, in a case of longer experiments, coronary insufficiency with arteriosclerosis.

Footnote

1. Candidate in Medical Sciences (Hospital Therapy Administration of the Child Health Medical Institute, Leningrad, and the K. M. Bykov Department of General Physiology of the Research Institute for Experimental Medicine of the Soviet Academy of Medical Sciences, Leningrad).

REFERENCES

1. Bredt, H., Ueber die Sonderstellung der tödlichen jugendlichen Coronarsklerose und die gewebliche Grundlage der akuten Coronarinsuffizienz [Special Status of Coronary Sclerosis in the Young and Tissue Foundation for Acute Coronary Insufficiency], Beitr. path. Anat. 110, 295 (1949).

2. Büchner, F., Allgemeine Pathologie. Pathologie als Biologie und als Beitrag zur Lehre vom Menschen [General Pathology. Pathology as Biology and as a Supplement to Antropology], 2 ed., Urban & Schwarzenberg, Munich-Berlin, 1956.

3. Chomulo, P. S., Ueber die Bedeutung der funktionellen Dauererregung des Nervensystems für die Entwicklung der Aortenlipoidose und von Myokardläsionen bei Kaninchen [Importance of Prolonged Functional Excitation of the Nervous System for the Development of Aortolipoidosis and Myocardial Lesions in Rabbits], Bull. exp. Biol. Med. 5/3, 9-44 (1961).

4. Doerr, W., Perfusionstheorie der Arteriosklerose [Perfusion Theory in Arteriosclerosis], Thieme, Stuttgart, 1963.

5. Gavyrin, V. A., Tropische Funktion von sympatischen Herznerven und Skelettmuskeln [Tropic Function of Sympathetic Cardiac Nerves and Skeletal Muscles], Inaugural dissertation, Leningrad, 1966.

6. idem and E. A. Moyiseyev, Ueber Veränderungen des Herzmuskels nach "Sympathisation" [Cardiac Muscle Changes following Sympathisation], Arch. Path. 23, 6-60 (1961).

7. Green, C. W., Control of the Coronary Blood Flow by Reflexes Arising in Widely Distributed Regions of the Body, Amer. J. Physiol. 113, 399 (1935).

8. Lebedinskiy, A. V., V. I. Medvedyev and I. A. Peymer, Bedeutung von Coronargefässen für die Pathogenese der Coronarinsuffizienz [Importance of Coronary Vessels for the Pathogenesis of Coronary Insufficiency], Leningrad, 1953.

9. Meessen, H., Ueber den plötzlichen Herztod bei Frühsklerose und Frühthrombose der Coronararterien bei Männern unter 45 Jahren [Sudden Death from Heart Attack in Early Sclerosis and Early Thrombosis in Men under 45], Z. Kreisl.-Forsch. 36, 185 (1944).

10. Müller, E., Die tödliche Coronarsklerose bei jüngeren Männern [Fatal Coronary Sclerosis in Younger Men], Beitr. path. Anat. 110, 103 (1949).

11. Reitman, S. and S. Frankel, A Colorimetric Method for the Determination of Serum Glutamic Oxalacetic and Glutamic Pyruvic Transaminases, Amer. J. Clin. Path. 28, 59 (1957).

12. Selye, H., Prophylaxe der Herznekrosen durch chemische Mittel [Drugs in the Prophylaxis of Coronary Necroses], Meditsina, Moscow, 1961.

13. Shutova, N. T., Zur Pathogenese der Störungen des Cholesterinumsatzes, In: Fragen der pathologischen Physiologie des Herzgefasssystems. Sammlung von Werken des Kinderheilinstitutes [Pathogenesis of Cholersterol Metabolism Disturbance,

in: Problems of the Pathological Physiology of the Cardiovascular System. Collection of the Works of the Child Health Institute, Leningrad, 1958, pp 5-21.

14. idem, Experimentelle Forschung zur Pathogenese von Störungen des Cholesterinumsatzes in der UdSSR. Veröff. der 3. Unionskonferenz [Experimental Research in the Pathogenesis of Cholesterol Metabolism Disturbances in the Soviet Union. Publication of the III All-Union Conference], 1963, pp 140-107.

15. Tyavokin, V. V., Ueber experimentelle Arteriosklerose und Störungen der Coronarblutzirkulation bei Beweglichkeitsbeschränkung von Kaninchen. In: Arteriosklerose [Experimental Arteriosclerosis and Disturbances in Coronary Blood Circulation in the Immobilization of the Rabbit, in: Arteriosclerosis], Leningrad, 1965, p.184.

16. idem, Experimentelles Verfahren zur Erzeugung von Coronarinsuffizienz [Experimental Procedure for Inducing Coronary Insufficiency], Pathologische Physiologie und experimentelle Therapie 1, 77-78 (1966a).

17. idem, Wirkung der Bewegungseinschränkung von Kaninchen auf die Entwicklung der experimentellen Cholesterinatherosklerose. In: Probleme der Pharmakologie und der experimentellen Pharmatherapie [Effect of Rabbit Immobilization on Development of Experimental Cholesterol Atherosclerosis, in: Problems of Pharmacology and Experimental Pharmacotherapy], Leningrad, 1966b, pp 80-83.

18. idem, Experimentelle Atherosklerose nach Bewegungseinschränkung von Kaninchen [Experimental Atherosclerosis following Rabbit Immobilization], Cor et vasa (Prague) 9/1, 65-72 (1967a).

19. idem, Arteriosklerose beim Kaninchen nach Bewegungseinschränkung [Arteriosclerosis in the Rabbit following Immobilization], Bull. exp. Biol. Med. 2, 19-22 (1967b).

20. idem in I. V. Davydovskiy, Arteriosklerose als Altersproblem [Arteriosclerosis as a Problem of Aging], Kardiologiya 8, 143-144 (1967).